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THE PATENTS ACT, 1970

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It is hereby certified that annexed hereto is a true copy of Provisional Specification filed on 05.08.2003 of the extract of Patent Application No. 639/CHE/2003 by M/s. MATRIX LABORATORIES LTD., an Indian Company, registered office at 1-1-151/1, IV Floor, Sairam Towers, Alexander Road, Secunderebad-500 003, Andhra pradesh, India.

.....In witness thereof

I have hereunto set my hand

Dated this the 24<sup>th</sup> day of August, 2004  
02<sup>nd</sup> day of Bhadrapada, 1926 (Saka)

M. s. Venkataraman

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THE PATENTS ACT, 1970

( 39 OF 1970 )

PROVISIONAL SPECIFICATION

( See Section 10 )

TITLE OF INVENTION

**"An improved process for the preparation of Moxifloxacin "**

2. Matrix Laboratories Ltd, with its registered office at 1-1-151/1 , IV Floor , Sairam Towers, Alexander Road, Secundrabad, 500003, India an Indian Company

The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

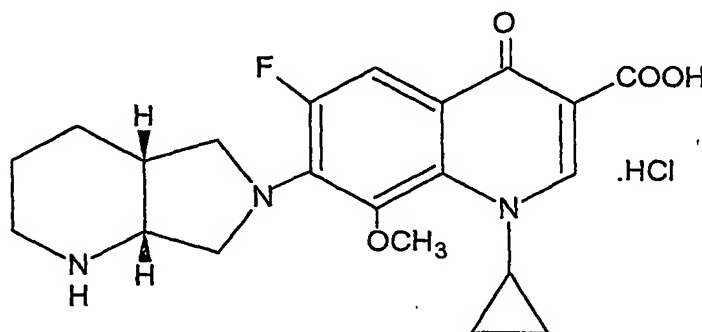
05-08-03 639 / CHE / 2003

### Field of the Invention

The present invention relates to a process for preparation of Moxifloxacin hydrochloride, using a novel intermediate namely (4aS-Cis)-(1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate.

### Background of the Invention

Moxifloxacin Hydrochloride namely (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0] non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid hydrochloride has the formula



**Moxifloxacin Hydrochloride**

Moxifloxacin is a fluoroquinolone broad spectrum antibacterial particularly against Gram-positive bacteria significantly better than those of Sparfloxacin and Ciprofloxacin that was disclosed in EP No 350,733 and EP No 550,903. Moxifloxacin has activity against Gram-negative and Gram-positive organisms, including *Streptococcus pneumonia*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, particularly against the respiratory disease-causing pathogens like *Mycoplasma pneumonia*, *Mycobacterium tuberculosis*, *Chlamydia pneumoniae* and the activity shown to be unaffected by B-lactamases.

US Patent No 5,157,117 discloses (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate and a process for its preparation by reacting the ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with Boric acid and acetic anhydride in presence of zinc chloride and conversion to gatifloxacin hydrochloride.

Other hydrates known are the anhydrous and monohydrate. US Patent No. 5,849,752 discloses the monohydrate of moxifloxacin hydrochloride and its

preparation by treating the anhydrous crystalline form with ethanol/ water mixtures.

The prior art disclosed in European Patent No's EP 350,733, EP 550,903 and EP 657,448 discloses the preparation of moxifloxacin hydrochloride involving the condensation of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid or its esters with (S,S) 2,8-Diaza bicyclo[4.3.0]nonane in presence of a base followed by conversion to hydrochloride at higher temperatures leading to the desired moxifloxacin along with its positional isomer namely (4aS-Cis)-1-cyclopropyl-6-(2,8-diazabicyclo [4.3.0]non-8-yl)-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid as a major impurity. As the impurity and the moxifloxacin are positional isomers they are difficult to separate. Purification of moxifloxacin to free it of this isomer results in lower yields thereby increasing the product cost. Similarly methods described in the prior art involve the preparation of moxifloxacin and then its conversion to its hydrochloride thereby incorporating an additional step in the manufacturing process also leading to lowering of yields.

It is a long felt of the industry to provide high yielding and cost effective processes for the preparation of Moxifloxacin hydrochloride

### **Summary of the invention**

The main object of the present invention is to provide a high yielding and cost effective process for the preparation of moxifloxacin hydrochloride.

Another object of the invention is to provide a process for the preparation of moxifloxacin hydrochloride without the additional step of isolation of moxifloxacin.

Another object of the invention is to explore other hydrates of moxifloxacin hydrochloride

Another object of the invention is to provide the fingerprinting of moxifloxacin hydrochloride pseudohydrate prepared by the invented process.

Another object of the invention is to provide a process for the conversion of moxifloxacin hydrochloride pseudohydrate to moxifloxacin hydrochloride monohydrate

Another object of the invention is to provide a process for the preparation of novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate and its use in the preparation for moxifloxacin hydrochloride .

Another object of the invention is to provide fingerprinting of the novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-

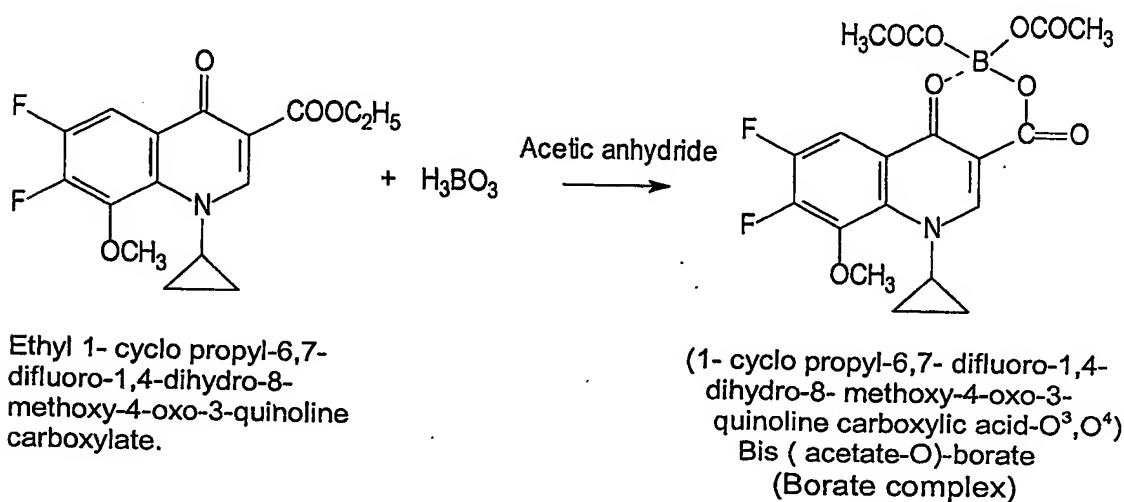
fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate using NMR, IR and x-ray diffraction analysis.

Another object of the invention is to provide a process for the preparation of (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate without using the catalyst and its use for the preparation of moxifloxacin hydrochloride.

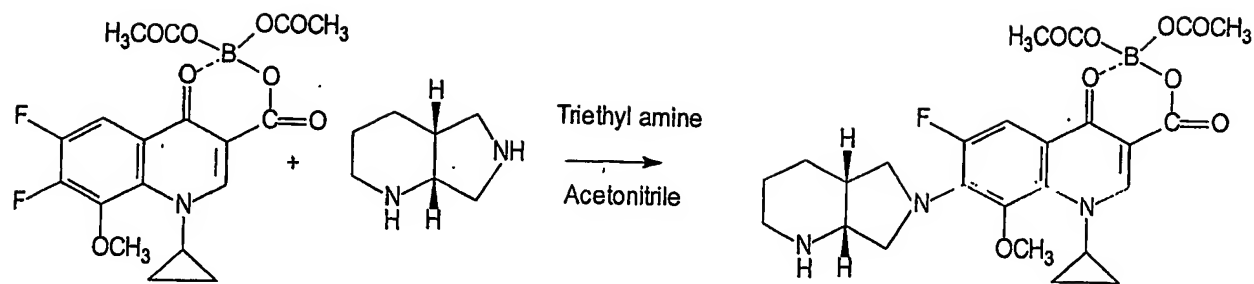
Accordingly, the present invention relates to a method for the preparation of Moxifloxacin hydrochloride from the ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate through a novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate. The reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with boric acid and acetic anhydride without using any catalyst gives (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ ) bis (acyloxy-O)borate which on condensation in presence of a base(s) with (S,S)-2,8-Diazabicyclo[4.3.0]nonane in organic polar solvent results the novel intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo [4.3.0] non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ ) bis (acyloxy-O) borate. This intermediate is reacted with hydrochloric acid in presence of solvent to give moxifloxacin hydrochloride pseudo hydrate. The moxifloxacin hydrochloride pseudohydrate is converted into moxifloxacin hydrochloride monohydrate by treating with hydrochloric acid in presence of ethanol.

The reaction scheme is given below:

#### Stage-I



## Stage-II

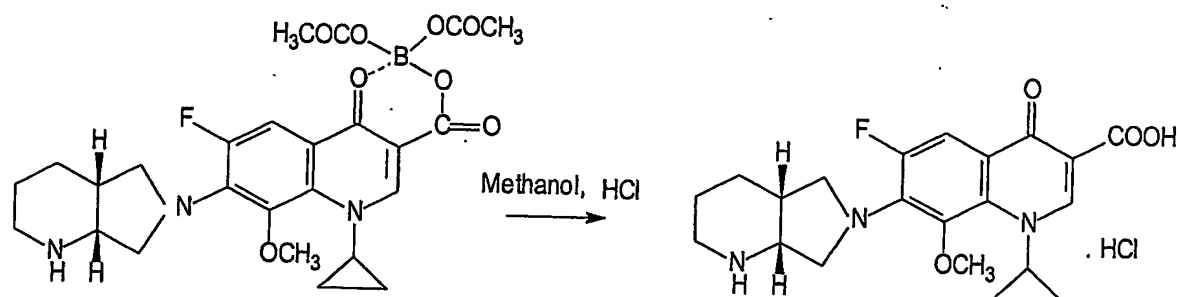


(1- cyclo propyl-6,7- difluoro-  
1,4- dihydro-8- methoxy-4-oxo  
-3-quinoline carboxylic acid-  
O<sup>3</sup>,O<sup>4</sup>)Bis ( acetate-O)-borate-  
(Borate complex)

[S,S]-2,8-diazabicyclo-  
[4.3.0]nonane

(1- cyclo propyl-6, fluoro-7(2,8-  
Diazabicyclo-nonane) 1,4-  
dihydro-8-methoxy-4-oxo-3  
quinoline carboxylic acid-  
( O<sup>3</sup>,O<sup>4</sup>) bis ( acetate-O)-borate

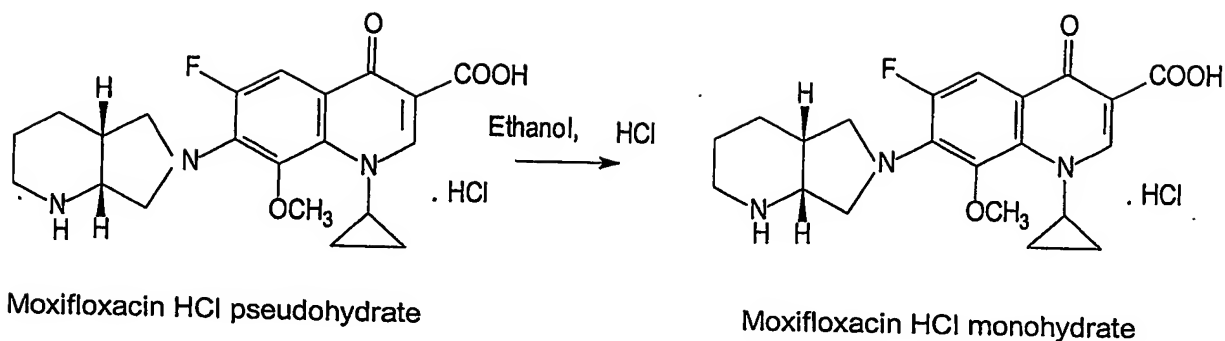
## Stage-III



(1- cyclo propyl-6, fluoro-7(2,8-  
Diazabicyclo-nonane) 1,4-  
dihydro-8-methoxy-4-oxo-3  
- quinoline carboxylic acid-  
( O<sup>3</sup>,O<sup>4</sup>) bis ( acetate-O)-borate

Moxifloxacin HCl pseudohydrate

#### Stage-IV



#### Brief description of the drawings

- Fig.1: X-ray diffraction pattern of the (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O) borate.
- Fig.2: FTIR spectrum of the (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate
- Fig.3: NMR spectrum of the (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo [4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid- $O^3, O^4$ )bis (acyloxy-O)borate
- Fig. 4: FTIR spectrum of the moxifloxacin hydrochloride psuedohydrate
- Fig. 5: X-ray diffraction pattern of the moxifloxacin hydrochloride psuedohydrate
- Fig. 6: FTIR spectrum of the moxifloxacin hydrochloride anhydrous
- Fig. 7: X-ray diffraction pattern of the moxifloxacin hydrochloride anhydrous
- Fig. 8 : FTIR spectrum of the moxifloxacin hydrochloride monohydrate
- Fig.9 : X-ray diffraction pattern of the moxifloxacin hydrochloride monohydrate

### Detailed description of the Invention

The process of the present invention comprises steps as:

- Reaction of ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate with a mixture of boric acid and acetic anhydride at temperature above 50°C without the use of catalyst
- Separation of (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate by cooling to low temperature followed by dilution with water
- Isolation and drying of the (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>) bis (acyloxy-O)borate
- Condensation of (1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate with (S,S)-2,8-diazabicyclo[4.3.0]nonane in presence of base(s) in organic polar solvent(s)
- Optional Isolation of the novel intermediate after completion of reaction (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-o)borate
- Optionally without isolation of the intermediate, directly proceeding to the preparation of moxifloxacin hydrochloride by reaction with hydrochloric acid in a solvent
- Isolation and drying of the product moxifloxacin hydrochloride pseudohydrate
- Optionally treating the moxifloxacin hydrochloride pseudohydrate with hydrochloric acid in ethanol to get moxifloxacin hydrochloride monohydrate

The prepared 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate is a hydrate and the novel intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate is anhydrous, characterized by chemical analysis NMR, IR spectrum and XRD.



The moxifloxacin hydrochloride pseudohydrate prepared by the process of this invention exhibits some novel characteristics such as water content varying from 0.5% to 1.0%, immediately on preparation and drying but absorbing moisture when exposed to atmosphere at varying humidity. However the XRD characteristics and IR patterns of the pseudohydrate as prepared remains substantially unaltered as illustrated in fig 4 & 5.

The starting materials ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate and [S,S]-2,8-diaza bicyclo[4.3.0]nonane are prepared by literature reported methods.

Acetic anhydride is heated to about 70°C, and boric acid is added in lots. The reaction mass is stirred for about 1hr to about 2 hrs at temperatures of about 70°C - about 125°C, preferably at about 110°C to - about 120°C, cooled to temperature of about 60°C - about 100°C, preferably to about 70°C. To this mixture, ethyl(1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate is added, the temperature raised to about 90°C - about 120°C, preferably to about 100°C to about 110°C and mixed for about 1hr to about 5 hrs preferably for about 1 hr. The reaction mass is cooled to temperature below 35°C, preferably to about 0°C - about 20°C, preferably to about 0°C followed by addition of cold water and then mixed for about 1 to about 4 hrs. The product formed is separated by conventional means, washed with water and dried to obtain 1-cyclopropyl-6, 7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate.

(1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate is suspended in organic polar solvents preferably DMSO, DMF, acetonitrile, ethanol and mixed with [S,S]-2,8-Diaza bicyclo[4.3.0]nonane in presence of organic, inorganic base(s) preferably triethyl amine, DBU, diisopropylethyl amine, potassium carbonate at temperatures about 20°C - about 120°C, preferably at about 60°C - about 80°C for about 1 hr to about 6 hrs. After the completion of reaction the reaction mass is cooled. The novel intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate is isolated by removal of solvent under vacuum below 60°C preferably at about 40°C - 45°C followed by addition of the hydrocarbons preferably hexane, heptane, cyclohexane, methyl cyclohexane, mixed for about 2 hrs, the product is filtered and dried.

Alternatively it is possible to proceed to the preparation of moxifloxacin hydrochloride pseudohydrate without the isolation of the intermediate (4aS-Cis)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate as follows:

The reaction mass is diluted with short chain alcohol, with an optional step of the removal of insolubles if any, adjusting the pH of the reaction mass to acidic with hydrochloric acid at temperatures below 35°C preferably in the range of about

20°C to about 25°C and stirred for about 2 to about 6 hrs. The alcohol is selected from C-1 to C-4 alcohols preferably methanol and/or ethanol. The pH is adjusted to below 2.0 preferably between below 0.5 and cooled to below 15°C preferably between about 0°C to about 5°C and maintained for about 2 to about 6 hrs. The product is separated and dried to obtain moxifloxacin hydrochloride pseudohydrate.

In another embodiment of the invention, the isolated intermediate (4aS-Cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-O<sup>3</sup>,O<sup>4</sup>)bis (acyloxy-O)borate is converted directly to moxifloxacin hydrochloride by dissolving in short chain alcohol preferably ethanol, methanol, removing the insolubles if any, adjusting pH to below 2.0 preferably to below 0.5 with hydrochloric acid and maintaining for about 1hr to about 4 hrs preferably for about 2 hrs at temperatures in the range of about 20°C to about 25°C. After completion of reaction, the reaction mass cooled to below 15°C preferably in the range of about 0°C to about 5°C and maintained for about 2 to about 6 hrs. The product is separated and dried to obtain moxifloxacin hydrochloride pseudohydrate.

Moxifloxacin hydrochloride pseudohydrate upon mixing with hydrochloric acid in presence of ethanol at temperature obtains moxifloxacin hydrochloride monohydrate.

The invention is now illustrated with a few non-limiting examples.

## **EXAMPLE - I**

### **Stage-1**

Acetic anhydride (175 gms) is heated to 70°C and boric acid (30 gms) is slowly added lot wise in a temperature range of 70°C to 90°C. The temperature is then raised, maintained under reflux for 1 hr followed by cooling to about 70°C. Ethyl-1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (100 gms ) is added under stirring. The temperature is then raised and maintained for 1 hr in the range of 100°C to 105°C. The reaction mass is cooled to 0°C, chilled water (400 ml) is added slowly followed by cold water (600 ml) at temperature 0°C to 5°C and maintained for 2 hrs at 0°C to 5°C. The product which is a boron acetate complex is filtered, washed with water (500 ml) and dried at 55°C to 60°C under vacuum to constant weight. The dry wt is 130.0 gms corresponding to yield of 95.2%

### **Stage – 2:**

The boron acetate complex (130 gms) prepared in stage 1 is suspended in acetonitrile (650 ml), and [S,S]-2,8-diazabicyclo[4.3.0]nonane (47 gms) and triethyl amine (72.9 gms) are added. The temperature is raised to reflux and maintained for 1 hr. at reflux, followed by cooling to about 40°C. The solvent is

removed under vacuum at temperature below 40°C, and n-hexane (200 ml) is added. After maintaining the reaction mass for 1 hr at room temperature the product is isolated by filtration followed by washing of the wet cake with n-hexane. The product is dried at about 45°C to about 50°C to constant weight. Dry wt of the novel intermediate is 117.0 gms corresponding to yield of 71.5%.

Elemental analysis: C: 56.42%, H: 5.62%, N: 7.76% and the calculated values for the intermediate, formula  $C_{25}H_{29}BFN_3O_8$  C: 56.6%, H: 5.47%, N: 7.92%

IR Spectrum (KBr,  $cm^{-1}$ ): 3415, 3332, 2936, 1718, 1630, 1573, 1526, 1445, 1273, 1042, 935, 860, 798, 682

$^1H$  NMR (200 MHz,  $CDCl_3$ , ppm): 9.00 (1H), 7.82 (1H), 4.12 (4H), 3.57 (3H), 3.43 (4H), 3.07 (2H), 2.75 (2H), 2.4 (1H), 2.1 (6H), 1.84 (2H), 1.6 (1H), 1.31 (2H)

Mass Spectrum ( $M^+$ ): 530.3 [ $M^+H$ ], 470.2 [ $M^+ - CH_3COOH$ ], 428.2 [ $M^+ - (CH_3CO)_2O$ , 100%], 402.2, 388.2

### Stage -3:

The intermediate (117 gms) prepared stage-2 is dissolved in ethanol (600 ml) by stirring for about 30 min. at room temperature and the insolubles if any are filtered off. pH of the filtrate is adjusted to about 0.5 by addition of hydrochloric acid at room temperature and maintained for 2 hrs. The reaction mass is cooled, and maintained for two hrs, at about 0°C to about 5°C. The product is filtered, washed with chilled ethanol (50 ml) and dried at about 50°C to about 55°C till constant weight.

The dry weight of the moxifloxacin hydrochloride pseudohydrate is 87.5 gms corresponding to yield of 91.0%. Water content of the product by KF is 0.64% w/w.

X-ray diffraction pattern data are given in Table-1

## EXAMPLE - II

### Stage- 2

The boron acetate complex (130 gms) prepared in stage-1 of Example-1 is suspended in acetonitrile (650 ml) and [S,S]-2,8-Diazabicyclo[4.3.0]nonane (47 gms) & triethyl amine (72.9 gms) are added. Temperature of the reaction mass is raised to reflux, maintained for 1 hr. at reflux and cooled to room temperature. Methanol (600 ml) is added and maintained for 30 min at room temperature to obtain a clear solution. The solution is filtered to remove insolubles if any and pH of the filtrate is adjusted to about 0.5 with hydrochloric acid (57.5 gms). The reaction mass is maintained for 2 hrs at temperature in the range of about 20°C to about 25°C, cooled to 0°C followed by maintaining the reaction mass at about

0°C to about 5°C for 2 hrs. The product is filtered, washed with methanol (50 ml) and dried at about 50°C to 55°C until constant weight.

Dry wt of the moxifloxacin hydrochloride pseudohydrate is 88 gms corresponding to yield of 68.7%.

#### EXAMPLE – III

Moxifloxacin hydrochloride (50 gms) prepared as above is suspended in a mixture of ethanol (250 ml) and hydrochloric acid (25 ml). Raised the temperature, maintained for two hrs at 40°C to 45°C followed by cooling to about 25°C. The product is filtered and dried under vacuum at 50–55°C until become constant weight.

Dry wt of Moxifloxacin hydrochloride monohydrate is 46 gms corresponding to yield of 90.5%.

The IR spectral data and XRD pattern are identical with available moxifloxacin hydrochloride monohydrate.

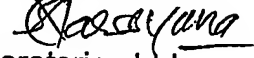
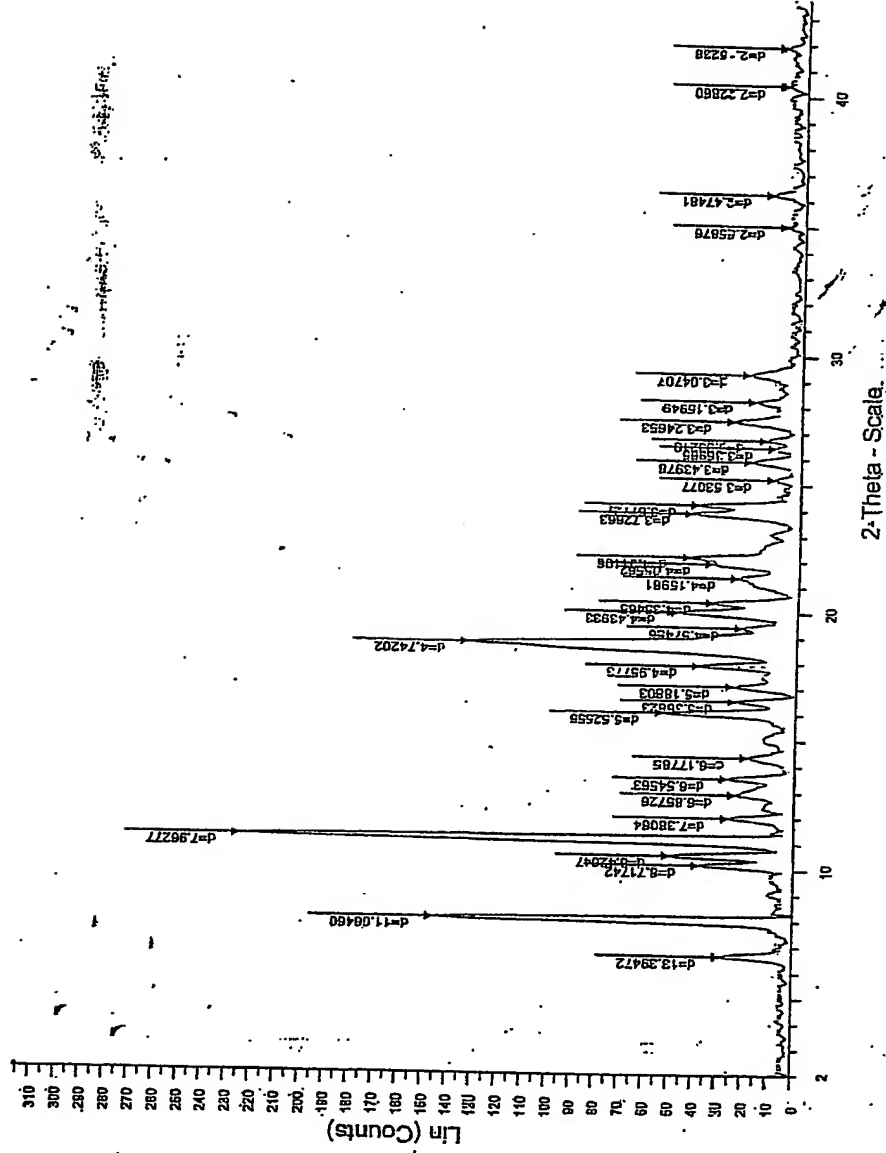
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Table-1

FTIR PEAKS OF MOXIFLOXACIN HYDROCHLORIDE			
S.No	PSEUDOHYDRATE	MONO HYDRATE	ANHYDROUS
1	3669	3530	3527
2	3357	3472	3469
3	2950	2925	2929
4	2894	2525	2524
5	2548	2456	
6	1730	2427	2427
7	1708	1709	1709
8	1623	1623	1621
9	1515	1516	1512
10	1456	1456	1452
11	1373	1395	
12	1354	1372	1371
13	1326	1353	1353
14	1183	1185	1186
15	1046	1046	1048
16	1028	994	994
17	938	938	938
18	875	875	709
19	835	835	834
20	804	804	804
21	722	722	722

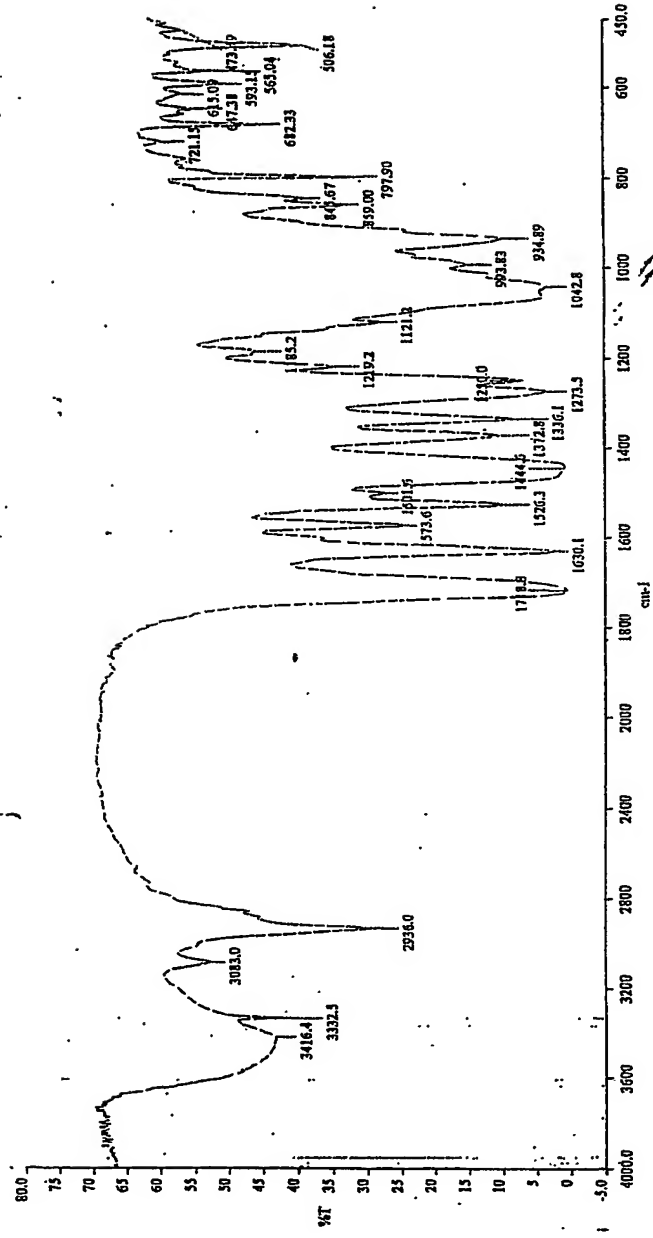
S.No	PSEUDOHYDRATE	MONO HYDRATE	ANHYDROUS
1	5.8	5.7	5.8
2	7.2	8.3	8.6
3	8.6	10	10.2
4	10.4	11.4	11.5
5	12.4	13.3	13.5
6	13.3	14.3	14.3
7	14.6	15.5	15
8	14.9	16.9	15.7
9	15.2	17.3	17.2
10	16.7	17.8	17.4
11	17.3	18.4	18.2
12	17.9	19.5	18.8
13	18.7	20.2	19.2
14	19.8	23.5	19.5
15	21.7	24	20.6
16	22.4	26.4	
17	24.7	26.6	21.5
18	25.2	27.3	22.5
19	25.8	29	
20	26.6	31.3	
21	27	35	
22	27.4	36.6	
23	27.9	38.6	
24	28.4	39.2	
25	29	43.2	
26	30		
27	31.6		
28	32.3		
29	35		
30	37.6		
31	39.1		
32	41.3		
33	41.9		
34	43.9		



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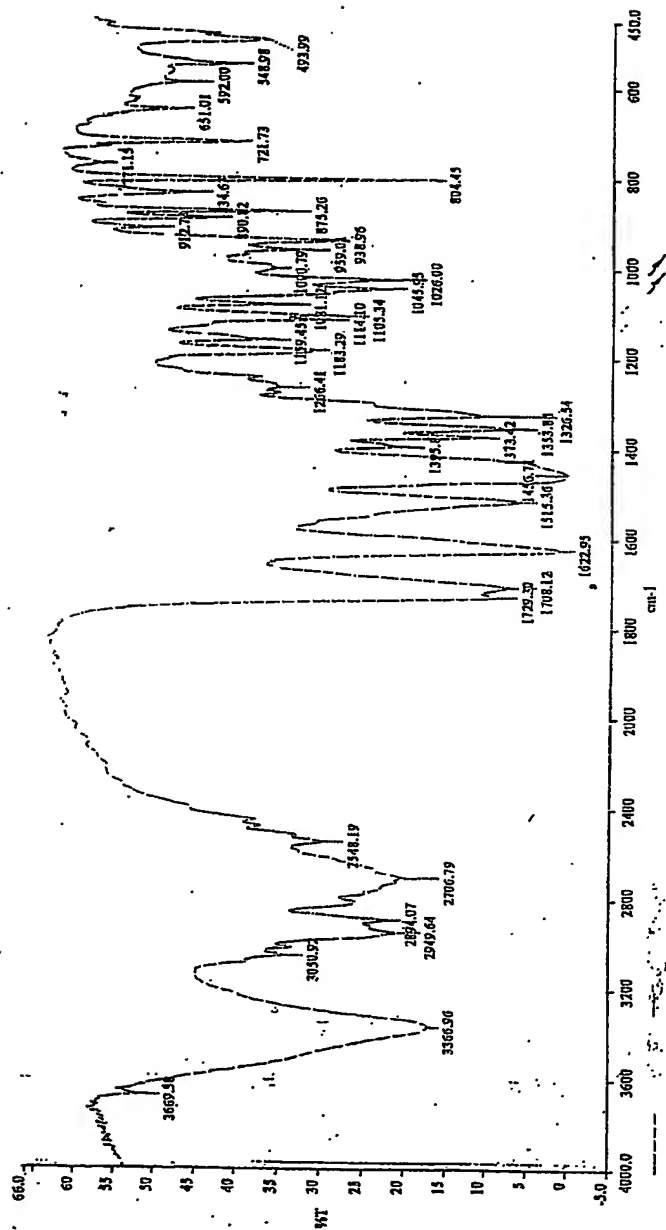
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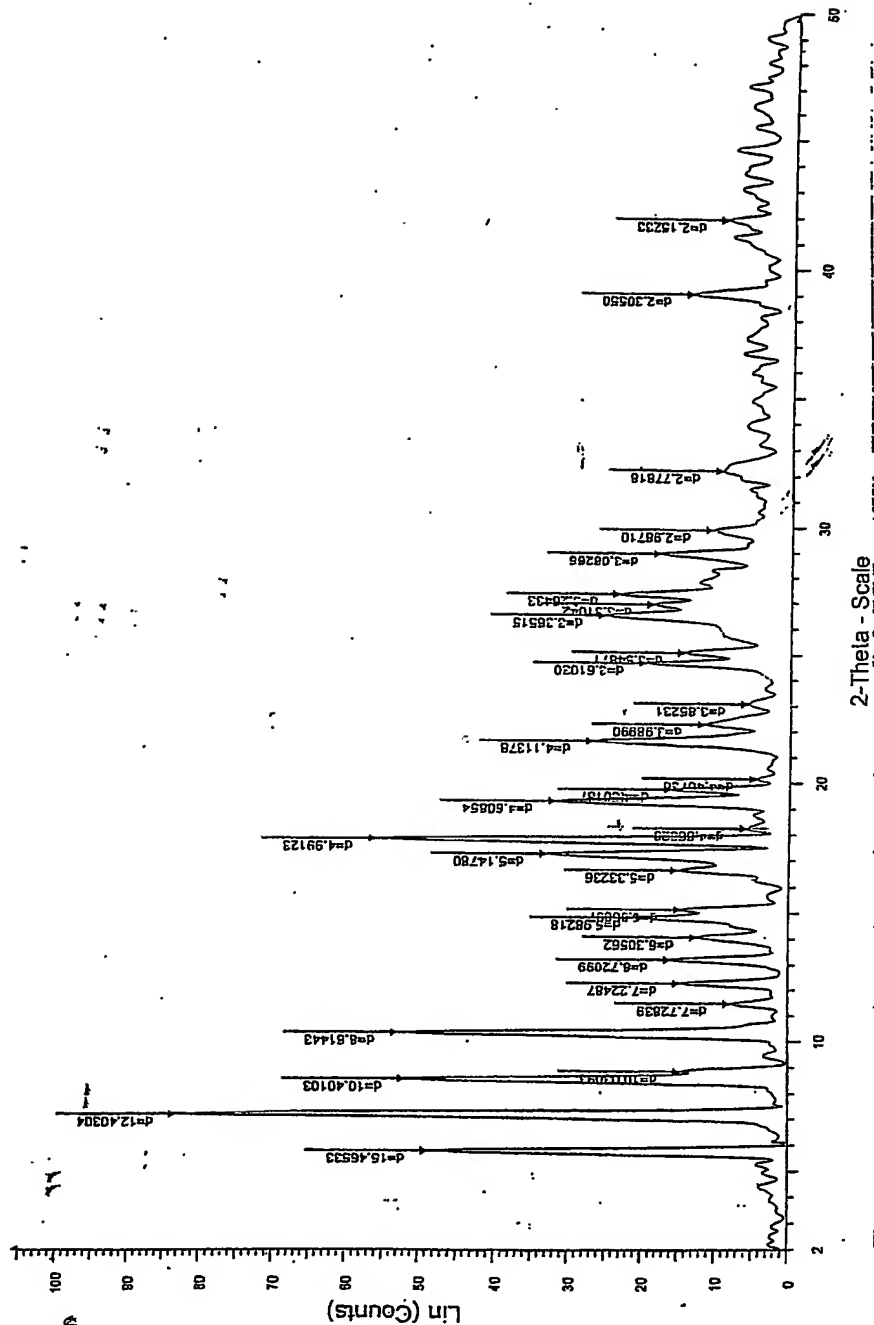
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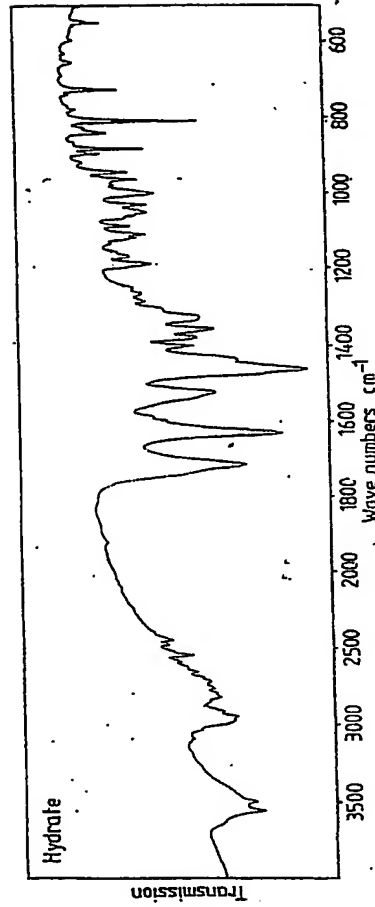
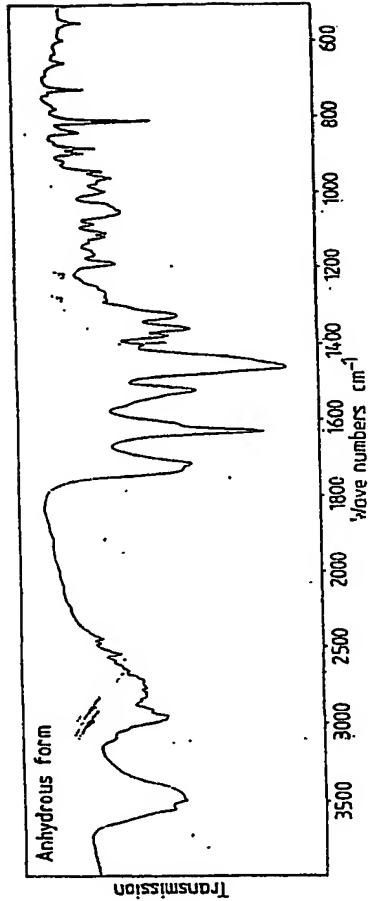




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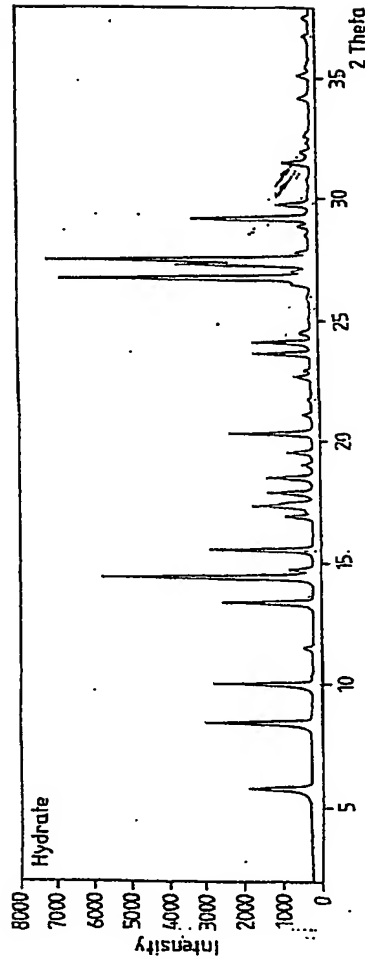
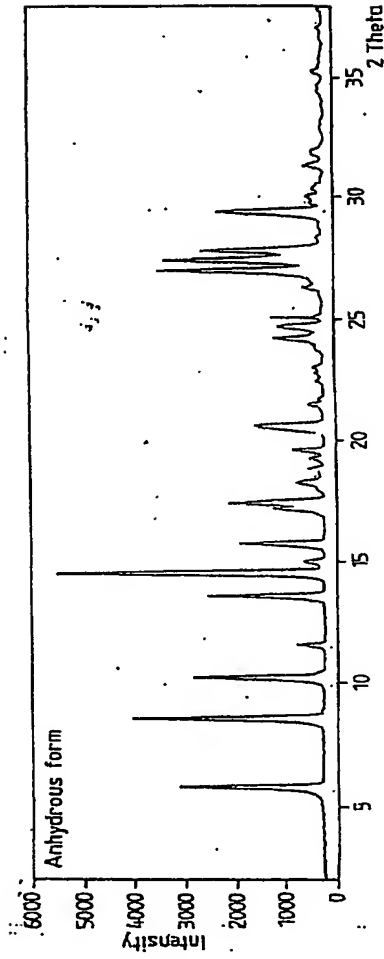
Applicant *Salvino*  
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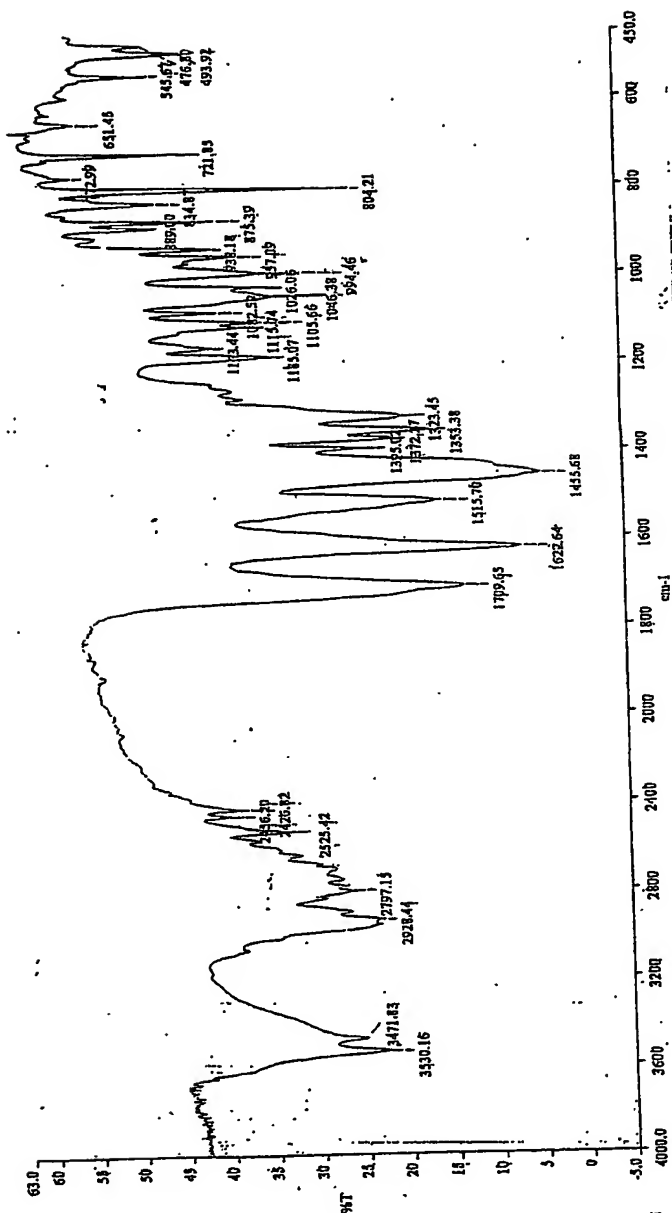
Applicant *Alexander*  
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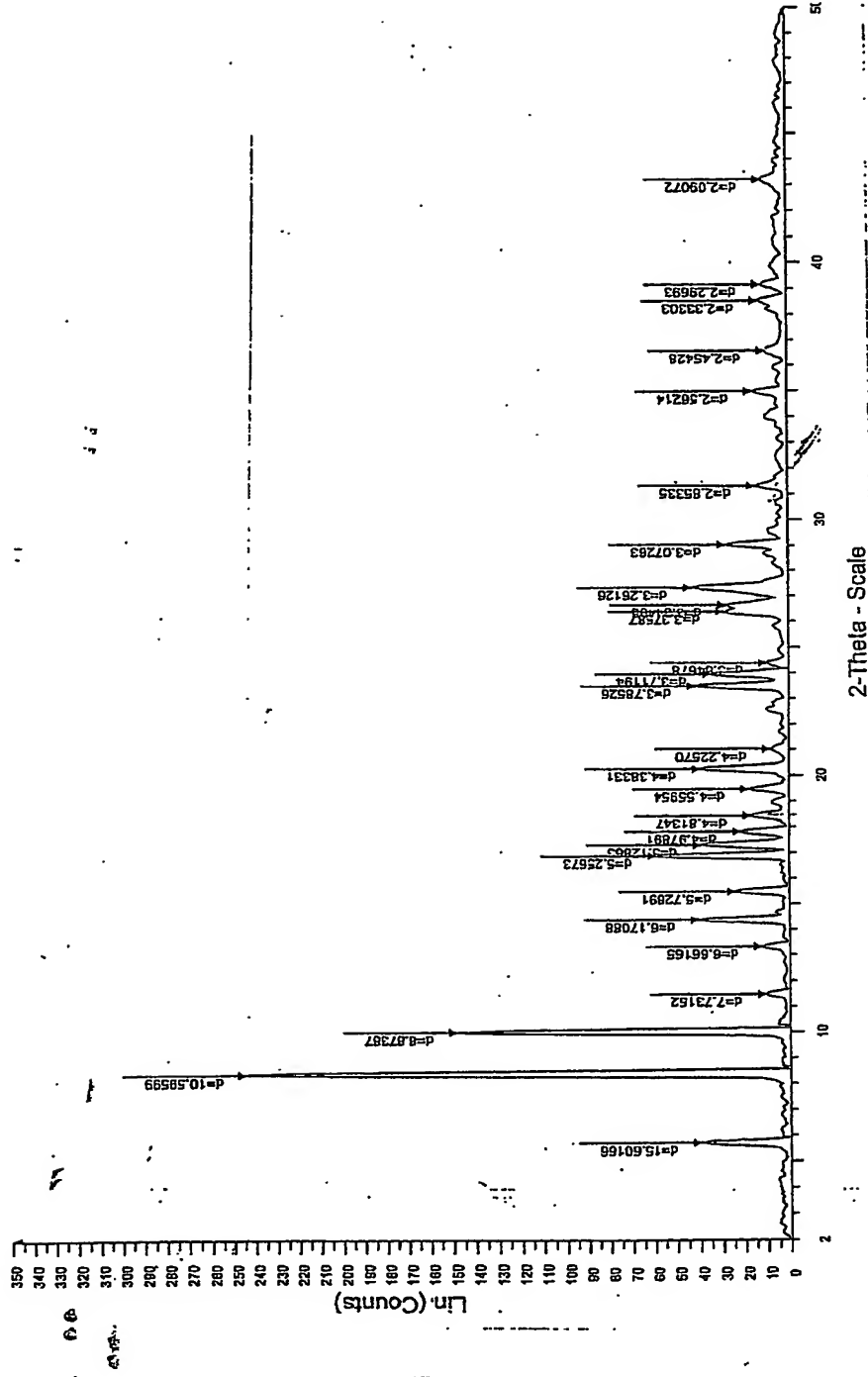
Sheet No 07



Applicant *Shreeya*  
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Applicant *Alexandra*  
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Applicant *Asayano*  
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